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QUARLES & BRADY LLP
33 E. MAIN ST, SUITE 900
P.O. BOX 2113
MADISON, WI 53701-2113

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,835	THOMPSON ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,8,9 and 11-24* is/are pending in the application.

4a) Of the above claim(s) *11-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

CLAIMS 1-2, 4-6, 8-9, & 11-24 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 6/7/2007 has been received and entered into the application. Accordingly, claims 1-2, 5-6, and 8-9 have been amended and claims 3, 7, and 10 have been cancelled. Claims 11-24 remain withdrawn from further consideration as being drawn to non-elected subject matter. Accordingly, claims 1-2, 4-6, and 8-9 are presently under examination and are the subject of this Office Action.

In view of the above amendments, the rejection of claims 1, 3-5, 7-8, and 10 under 35 U.S.C. 112, 2nd Paragraph has been overcome and thus is withdrawn. Also, the amendments and Applicants' remarks have overcome the rejections not reiterated herein from the previous Office Action. Such rejections are hereby withdrawn. The following rejections are either reiterated or newly applied and constitute the totality of issues remaining in the present application.

In light of the new rejections being applied against the pending claims, this Office Action is Non-Final.

Response to Arguments

Applicant's arguments with respect to claims 8-10 (35 U.S.C. § 112, 1st Paragraph) have been considered but are moot in view of the new ground(s) of rejection.

Applicant's arguments filed 6/7/2007 have been fully considered but they fail to persuade the Examiner of an error in his determination that the instantly claimed methods would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Firstly, Applicants assert that is improper for the Examiner to use Applicants' own disclosure for the proposition that the anti-androgenic activity of chromanol-derived moiety is a newly

discovered property. However, the Examiner respectfully submits that the citation of Applicants' disclosure was not a basis for the present rejection (*i.e.*, the Examiner was not relying on Applicants' disclosure to form the basis of the rejection). It is noted that the Examiner never indicated that the prior art taught the anti-androgenic activity of the claimed compounds. Secondly, Applicants argue that the references fail to provide explicit motivation to administer PMCol to inhibit prostate cancer cells. However, Applicants are reminded that explicit motivation is not required for a finding of obviousness. In response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, the Examiner has relied on the teachings of two individual references that, when combined, form the basis for the *prima facie* case of obviousness. This finding, based on an analysis of the prior art and in view of the *Graham* factors set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), is based on the facts presented in the prior art. For example, it is a finding of fact that α-tocopherol inhibits the growth of androgen-dependent prostate cancer cells as evidenced in Gunawardena *et al.* Gunawardena *et al.* also teach that the anti-cancer activity of α-tocopherol could be due to its anti-oxidant activity. However, the fact that α-tocopherol was only *minimally* effective against androgen-*independent* prostate cancer cell growth would lead the skilled artisan to believe that α-tocopherol may also have anti-androgenic activity. It is also a finding of fact that PMCol is a more potent anti-oxidant and is more hydrophilic than α-tocopherol, has potent radical scavenging activity, and is a potent inhibitor of nuclear factor-κB (NF-κB) activity. All of these

findings lead the skilled artisan to the reasonable expectation that PMCol would be as effective, if not more effective, than α-tocopherol in inhibiting androgen-dependent prostate cancer cell growth.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5, and 8-9 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to

practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

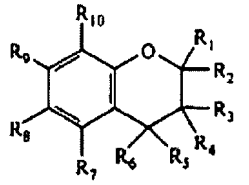
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

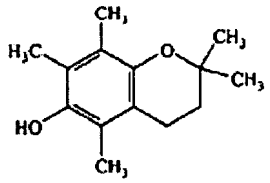
1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The invention relates to the treatment or prevention of androgen-dependent prostate cancer in a human patient comprising administering a compound having the structure:



wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9 and R_{10} are independently selected from the group consisting of unsubstituted C_1-C_3 alkyl group, C_1-C_3 alkyl substituted with one or more of halogen, hydroxy, alkoxy carbonyl, nitro, thio and thioalkyl, and H; and wherein R_8 is an OH. Claim 9 relates to the prevention of androgen-dependent prostate cancer in a human patient comprising administering a compound having the structure:



The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies

inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354), Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431), and Singh *et al.* (Endocrine-Related Cancer, 2006, vol. 13, pages 751-778).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*).

Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

Singh *et al.*, also cited for evidentiary purposes, review the mechanism of action of novel agents for prostate cancer chemoprevention. It is noted that "chemoprevention" as used in Singh *et al.* relates to prevention, suppression, and/or reversal of early and/or late stages of cancer growth (page 751). Optimal therapeutic response in prostate cancer patients has been compounded by the problem of early diagnosis and with the emergence of androgen independence during commonly used anti-androgen therapy (Abstract). While many agents have been tested for chemoprevention in prostate cancer patients, there is no known agent that can prevent prostate cancer from occurring (pages 767-768).

These articles plainly demonstrate that the art of treating prostate cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to prevent prostate cancer.

2. The breadth of the claims

The claims vary in breadth; some (such as claims 1, 5, and 8) are extremely broad, reciting the treatment or prevention of androgen-dependent prostate cancer with a genus of compounds having nine variable positions, which can each independently be substituted with a C_1-C_3 alkyl optionally having one or more different substituents. Others, such as claim 9, are narrower, reciting a specific species of the claimed genus of compounds. All, however, are extremely broad insofar as they disclose the general treatment or prevention of androgen-dependent prostate cancer with the same compounds, only one of which has actually been tested.

3. The amount of direction or guidance provided and the presence or absence of working examples

Firstly, it is noted that the present invention is based on the inventor's discovery that the chromanol-derived moiety of vitamin E possesses potent anti-androgenic activity in androgen-dependent cells (page 5, lines 11-13). In this regard, one compound was shown to have such activity. This compound, 2,2,5,7,8-pentamethyl-6-chromanol (PMCol), is a commercially available compound known for its antioxidant activity. Based on the anti-androgenic activity of this one compound *in vitro*, Applicant claims methods of treating and preventing androgen-dependent prostate cancer, in a human patient, with a plethora of structurally related compounds.

The specification provides no direction or guidance as to how one skilled in the art would make the compounds of the present invention. In this regard, Applicant simply discloses that the anti-androgen compounds useful in the invention are either known or "obtainable through purification schemes and/or syntheses known to those of skill in the art" (page 15, lines 6-8). Applicant also cites an Advanced Organic Chemistry book (Carey *et al.*, 2001) that the skilled artisan could refer to in order to find methodologies for deriving compounds structurally related to PMCol (*id.* at lines 10-14). However, the claimed compounds may contain multiple, diverse functional groups. The synthesis of such compounds is not necessarily an easy task and may require multiple protection/deprotection steps in order to not cleave or modify reactive functional groups. While such protection and deprotection of functional groups are known in the art, determining exactly which protection strategy and deprotection strategy will not result in modification of chemical entities on the compound would require undue experimentation considering the scope of the claimed compounds. As noted *supra*, the only compound

exemplified and explicitly disclosed in the reference is a commercially available compound. Further, reference to a method of making α-CEHC is not seen as enabling the synthesis of the broad scope of the claimed compounds because α-CEHC only contains CH3 groups as substituents. None of the instantly claimed substituents are present.

The specification also provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat or prevent androgen-dependent prostate cancer with the plethora of compounds encompassed by the claims, particularly in humans. The direction concerning treating prostate cancer is found in the specification at pages 37-44, which merely provides cellular assays for determining the cell growth inhibitory effect of one compound of the invention (PMCol). An *in vivo* assay for determining the efficacy of the claimed compounds using an LNCaP xenograft model is provided at pages 50-52. No compounds were actually tested in this assay. Applicants describe formulations at pages 24-30. No doses useful in treating or preventing prostate cancer in human patients are provided. Applicant asserts that "optimum effective amounts can be readily determined by one of ordinary skill in the art using routine experimentation" (page 24, lines 17-18). However, considering the broad scope of the claimed compounds, it would not be "routine" to determine effective doses of the claimed compounds in human patients.

As noted *supra*, there is both an *in vitro* cellular assay and an *in vivo* assay described at pages 37-44 and 50-52 (with no data in the *in vivo* assay) and it is unclear if these assays correlate to the treatment of prostate cancer in human patients. For example, as discussed *supra*, *in vitro* and *in vivo* cancer models do not always correlate to effective treatment of the same cancer in human patients. There is no working example of treatment of androgen-dependent

prostate cancer in a human patient using the claimed compounds. Further, the androgen antagonist activity of one compound of the invention does not predictably correlate to clinical efficacy. Thus, there are no working examples correlating inhibition of the androgen receptor in cells with efficacy in the treatment of prostate cancer using the claimed compounds (*i.e.*, Applicant has not shown that inhibition of the androgen receptor with a compound of the invention correlates to *in vivo* anticancer efficacy with the same compound).

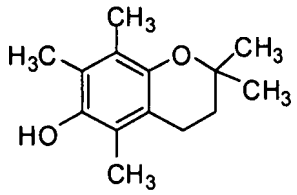
4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment and/or prevention for androgen-dependent prostate cancer as inferred in the claims and contemplated by the specification.

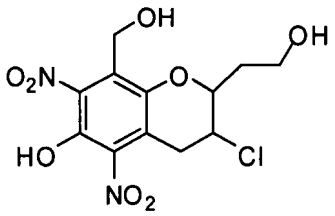
Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because PMCol has anti-androgenic activity *in vitro*, PMCol and compounds related to PMCol must therefore, *a priori*, be useful in the treatment and prevention of androgen-dependent prostate cancer in human patients. However, the claims encompass a multitude of compounds having a plethora of chemically and biologically distinct substituents. Applicants appear to have purchased PMCol

through a commercial vendor. No other compounds of the invention were made or tested, and Applicants have provided no guidance or direction on how such compounds could be made without undue experimentation. Thus, the one compound tested by Applicants does not correlate in scope with the claimed subject matter. For example, PMCol, the compound tested by Applicants, has the following structure:



PMCol



Compound A

PMCol was purchased and tested for anti-androgen activity in LNCaP cells by Applicants. Compound A is a hypothetical compound that is encompassed by the claims. This compound, and compounds like it, have not been synthesized or tested. One skilled in the art would not reasonably expect that Compound A would have similar activity to PMCol given the chemically and biologically distinct substituents present in each compound. Given the extremely diverse compounds encompassed by the claims and the limited examples provided in the specification, the skilled artisan cannot predict what structural features (other than those of the compound actually tested) are important for anti-androgen activity. In other words, the structure activity relationship demonstrated in the examples is limited to a very small sub-genus of compounds.

Determining if any particular claimed compound would inhibit androgen receptors *in vitro*, let alone treat or prevent prostate cancer in humans, would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue

experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

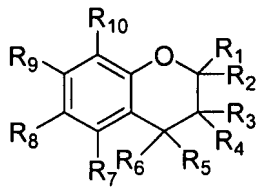
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Instant claims 1-2 and 4 are drawn to a method for inhibiting the growth of androgen-dependent tumor in a human and claims 5-6 are drawn to a method of delaying the progression of prostate cancer in a patient comprising administering a compound having the formula:



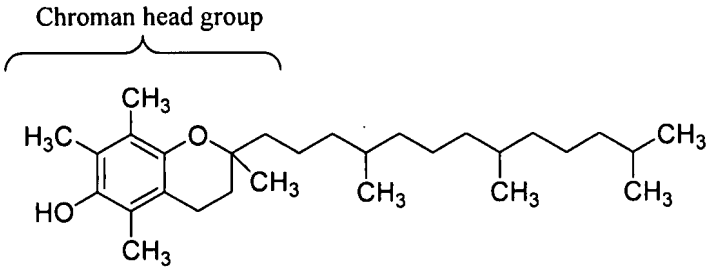
wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_9 and R_{10} are independently a substituted or unsubstituted C_1-C_3 alkyl group or H and R_8 is OH. The present rejection is limited to the obviousness of using the specific compound PMCol to treat prostate cancer.

Claims 1-2 and 4-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gunawardena *et al.* (The Prostate, 2000, vol. 44, pages 287-295) (cited by applicants) in view of Sheu *et al.* (Life Sciences, 1999, vol. 65, pages 197-206) (cited by applicants).

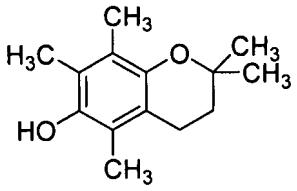
Gunawardena *et al.* disclose that vitamin E (α-tocopherol) and other antioxidants inhibit the growth of human prostate cancer cells through apoptosis (Abstract). The authors disclose that antioxidants have been associated with a reduced risk of cancer in various tissues, including the prostate (page 288, left column). Three prostate cancer cell lines, DU-145 (androgen-unresponsive), LNCaP (androgen-responsive) and ALVA-101 (androgen moderately responsive) were used to test the effects of several antioxidants, including α-tocopherol on cell growth in culture (*id.* at right column). α-Tocopherol produced significant growth suppression of ALVA-101 and LNCaP cells compared to control (page 289, left column). The authors further disclose that androgens increase oxidative stress in androgen-responsive but not androgen-unresponsive cells such as PC-3 (page 292, left column). Vitamin E did not cause growth inhibition of in the

androgen-unresponsive (DU-145) human prostate cancer cell lines, whereas it did significantly affect the growth of the androgen-responsive cell lines (*id.*). In summary, the authors conclude that the results suggest that antioxidants may retard human prostate cancer cell growth through mechanisms that activate apoptosis (page 292, right column).

Sheu *et al.* compare the activities of α-tocopherol and PMC (2,2,5,7,8-pentamethyl-6-hydroxychromane) on platelet aggregation and antioxidant activity (Abstract). PMC is the same compound recited in instant claims 2 and 6 and is disclosed to be a "potent antioxidant derived from α-tocopherol" (Abstract).



α-Tocopherol (Vitamin E)



PMC

PMC is more hydrophilic than other α-tocopherol derivatives and has potent radical scavenging activity (page 198). It is also taught in Sheu *et al.* that PMC is a potent inhibitor of nuclear factor-κB (NF-κB) activity (*id.*). PMC was shown to have greater antioxidant activity than α-tocopherol (page 204). The authors conclude that the antioxidant activities of PMC in various radical-mediated pathological events, particularly in *in vivo* situations, should be further studied (page 205).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and Content of the Prior Art:

In the instant case, the prior art teaches that α-tocopherol has activity in inhibiting androgen-dependent prostate cancer cell growth possibly due to its antioxidant activity. Sheu *et al.* demonstrate that the antioxidant activity of α-tocopherol is mainly due to the chroman head group (PMC vs. α-tocopherol).

Differences Between Prior Art and Claims:

The prior art differs from the instant claims in that it does not explicitly disclose that the instantly claimed compounds have anti-androgenic activity or inhibit prostate cancer cell growth.

Level of Ordinary Skill in the Art:

A person having ordinary skill in the art at the time of the present invention would generally be a medical chemist well practiced in the art of structure-activity relationships as they pertain to chemical modifications and biological activity.

Objective Evidence and Motivation:

In light of the above findings relating to the three *Graham* factors, the skilled artisan would have been motivated to administer PMCol (PMC) to patients having androgen-dependent prostate cancer. See, *e.g.*, *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of

unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." (emphasis in original)); *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). In this case, the prior art teaches that PMCol is a known derivative of α-tocopherol having potent anti-oxidant activity and that α-tocopherol inhibits androgen-dependent prostate cancer cell growth *in vitro*, possibly due in part to its anti-oxidant activity. The skilled artisan would recognize that the anti-oxidant activity of α-tocopherol is due to its chromanol head group as evidenced by Sheu *et al.* As such, using PMCol (PMC) to inhibit androgen-dependent prostate cancer cell growth would be the next logical step. Further, the fact that α-tocopherol only inhibited androgen-dependent prostate cancer cell lines would lead the skilled artisan to believe that α-tocopherol may have anti-androgenic activity in addition to its anti-oxidant activity.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to administer PMCol to patients having androgen-dependent prostate cancer. This is especially true given the correlation between anti-oxidant activity and inhibition of prostate cancer cell growth as taught in Gunawardena *et al.* (*i.e.*, oxidative stress induced by androgens in prostate cancer cells). Accordingly, the skilled artisan would have been highly motivated to administer the instantly claimed PMCol to prostate cancer patients, based on the reasonable expectation that structurally similar species usually have the same properties. See, *e.g.*, *Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also *Deuel*, 51 F.3d at 1558, 34 USPQ2d at 1214 ("Structural relationships may provide the requisite motivation or suggestion to modify known

compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."). In this case, PMCol is a more potent anti-oxidant, inhibits NF-κB, and is more hydrophilic than α-tocopherol. Since α-tocopherol inhibits androgen-dependent prostate cancer cell proliferation, the skilled artisan would predict, *a priori*, that a compound that is a better anti-oxidant, more hydrophilic, and that also inhibits NF-κB would be as effective, if not more effective, than the parent compound α-tocopherol in inhibiting androgen-dependent prostate cancer cell growth.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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James D. Anderson
Patent Examiner
AU 1614

August 28, 2007

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER